

Supplementary Note 1a: Members of the WTCCC2 Consortium

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Supplementary Table 1 Allele frequency, Hardy-Weinberg p-values, test of dominance and sex interaction for SNPs in Tables 1, 2 and 3.

Chr	rsID	Risk Allele	Other Allele	Control frequency (Risk allele)		Case frequency (Risk allele)		Control HW P-value		Cases HW P-value		Dominance (LRT P-value)		Gender effect (LRT P-value)		Replication					
				TASC	WTCCC2	Replication	WTCCC2	TASC	WTCCC2	TASC	WTCCC2	TASC	WTCCC2	TASC	WTCCC2	TASC					
1	rs11249215	A	G	0.47	0.51	0.47	0.50	0.54	0.50	0.88	0.97	0.50	0.20	0.059	0.58	0.16	0.019	0.26	0.63	0.71	0.082
1	rs11209026	G	A	0.93	0.94	0.94	0.95	0.97	0.96	0.96	0.79	0.24	0.14	0.40	0.84	0.010	1.0	0.24	0.043	0.34	0.92
1	rs11209032	A	G	0.33	0.32	0.33	0.38	0.37	0.36	0.35	0.065	0.24	0.98	0.90	0.91	0.61	0.13	0.82	0.030	0.94	0.51
1	rs2297909	G	A	0.68	0.71	0.68	0.70	0.74	0.73	0.78	0.67	0.61	0.17	0.16	0.97	0.069	0.11	0.90	0.43	0.22	0.77
2	rs10865331	A	G	0.37	0.41	0.37	0.44	0.46	0.45	0.67	0.076	0.71	0.59	0.73	0.71	0.77	0.52	0.68	0.50	0.39	0.46
4	rs4389526	A	T	0.63	0.64	0.64	0.66	0.68	0.67	0.79	0.49	0.92	0.96	0.21	0.88	0.70	0.13	0.57	0.45	0.87	0.99
5	rs10440635	A	G	0.60	0.57	0.59	0.63	0.62	0.61	0.57	0.11	0.76	0.40	0.23	0.35	0.55	0.65	0.33	0.22	0.81	0.88
5	rs10050860	C	T	0.77	0.80	0.77	0.81	0.83	0.82	0.97	0.13	0.18	0.11	0.0032	0.20	0.026	0.00033	0.67	0.78	0.26	0.77
5	rs30187	T	C	0.33	0.36	0.35	0.40	0.42	0.40	0.94	0.29	0.92	0.00065	0.019	6.4x10 ⁻⁸	0.0017	0.0028	1.3x10 ⁻⁵	0.94	0.34	0.71
5	rs6556416	C	A	0.67	0.69	0.68	0.71	0.72	0.71	0.41	0.55	0.44	0.79	0.091	0.97	0.95	0.21	0.46	0.82	0.92	0.56
6	rs13202464	G	A	0.066	0.047	0.066	0.46	0.47	0.44	0.75	0.59	0.73	<10 ⁻¹⁰⁰	<10 ⁻¹⁰⁰	<10 ⁻¹⁰⁰	1.5x10 ⁻²⁰	1.1x10 ⁻²¹	1.2x10 ⁻¹⁰	0.0031	0.10	0.0033
6	rs4349859	A	G	0.043	0.036	0.042	0.44	0.46	0.41	0.95	0.25	1.0	<10 ⁻¹⁰⁰	<10 ⁻¹⁰⁰	<10 ⁻¹⁰⁰	4.5x10 ⁻¹²	6.3x10 ⁻²³	1.3x10 ⁻⁸	0.026	0.30	0.079

9	rs10781500	T	C	0.42	0.41	0.43	0.46	0.45	0.45	0.73	0.36	0.76	0.46	0.45	0.71	0.68	0.34	0.82	0.029	0.19	0.77
12	rs11616188	A	G	0.43	0.44	0.42	0.50	0.50	0.44	0.32	1.4×10^{-5}	0.98	0.0026	0.00033	0.51	0.13	0.40	0.41	0.12	0.45	0.27
17	rs8070463	C	T	0.51	0.51	0.52	0.55	0.56	0.54	0.40	0.51	0.95	0.66	0.27	0.48	0.20	0.18	0.96	0.92	0.46	0.28
21	rs378108	G	A	0.48	0.47	0.49	0.53	0.53	0.51	0.95	0.070	0.87	0.99	0.57	0.78	0.66	0.12	0.91	0.46	0.28	0.37

Supplementary Table 2 Association results for the 49 SNPs that passed quality control in the replication analysis. P values are based upon likelihood ratio tests.

Chromosome	RsID	Position	Effect Allele	OR (95% CI)	P value
1	rs10903118	25167465	C	1.14 (1.06-1.23)	0.00070
1	rs11249215	25169771	A	1.15 (1.07-1.24)	0.00028
1	rs11465804	67475114	T	1.52 (1.26-1.84)	6.2x10 ⁻⁶
1	rs11209026	67478546	G	1.61 (1.34-1.93)	1.4x10 ⁻⁷
1	rs11209032	67512680	A	1.17 (1.08-1.27)	8.0x10 ⁻⁵
1	rs7546245	67523062	C	1.16 (1.07-1.25)	0.00028
1	rs11265622	152718044	A	1.05 (0.97-1.14)	0.19
1	rs4478801	152731196	G	1.05 (0.97-1.14)	0.21
1	rs378672	199152956	C	1.19 (1.09-1.29)	3.6x10 ⁻⁵
1	rs2297909	199226930	C	1.25 (1.15-1.36)	1.4x10 ⁻⁷
1	rs12118525	215454528	C	1.02 (0.94-1.11)	0.64
2	rs10865331	62404976	A	1.36 (1.26-1.47)	2.1x10 ⁻¹⁵
2	rs4851529	102013732	G	1.06 (0.98-1.14)	0.16
2	rs2310173	102030060	T	1.04 (0.96-1.12)	0.31
2	rs4141634	102043501	T	1.02 (0.95-1.1)	0.58
2	rs6543345	105837825	C	1.06 (0.93-1.2)	0.41
3	rs753294	55169996	G	1.07 (0.96-1.19)	0.22
3	rs17759800	55172660	G	1 (0.88-1.14)	0.96
4	rs6534625	81029021	G	1.09 (1.01-1.18)	0.029

4	rs4389526	81165499	A	1.1 (1.02-1.19)	0.019
4	rs4834244	113370008	C	1.02 (0.95-1.1)	0.55
4	rs4834249	113400470	T	1.03 (0.95-1.11)	0.48
5	rs13172042	35983288	G	1.05 (0.97-1.15)	0.22
5	rs1993879	35987897	C	1.04 (0.96-1.14)	0.35
5	rs10440635	40526547	A	1.1 (1.02-1.19)	0.017
5	rs4286721	40533361	A	1.12 (1.03-1.22)	0.0073
5	rs10050860	96147966	C	1.32 (1.2-1.46)	1.1×10^{-8}
5	rs30187	96150086	T	1.28 (1.18-1.39)	1.1×10^{-9}
5	rs13170045	96151541	G	1.35 (1.23-1.49)	7.7×10^{-10}
5	rs27710	96151953	A	1.28 (1.19-1.39)	7.6×10^{-10}
5	rs12522532	134478020	C	1.02 (0.94-1.11)	0.58
5	rs10045431	158747111	C	1.18 (1.09-1.29)	0.00011
5	rs6556416	158751323	C	1.17 (1.08-1.27)	0.00016
6	rs4959041	30185946	C	1.35 (1.24-1.47)	6.5×10^{-13}
6	rs2254556	31450610	G	2.29 (2.02-2.61)	3.8×10^{-42}
6	rs13202464	31452562	G	27.6 (23.86-31.93)	$<10^{-200}$
6	rs4349859	31473766	A	40.81 (34.96-47.64)	$<10^{-200}$
9	rs10781499	138386226	A	1.05 (0.97-1.13)	0.21
9	rs10781500	138389159	T	1.08 (1-1.17)	0.041
12	rs11616188	6373003	A	1.12 (1.04-1.21)	0.0036
13	rs598351	70223053	A	1.05 (0.92-1.19)	0.49
14	rs11846074	81269241	C	1.07 (0.99-1.17)	0.10

16	rs12923138	65790767	C	1.12 (1.04-1.2)	0.0035
16	rs7200919	65874101	A	1.07 (0.99-1.15)	0.11
16	rs12599580	66508114	C	1.09 (1.01-1.18)	0.027
17	rs9788973	11926299	C	1.03 (0.95-1.11)	0.49
17	rs11078050	11945976	G	1.01 (0.93-1.09)	0.85
17	rs8070463	43123835	C	1.1 (1.02-1.18)	0.015
17	rs4794067	43163827	T	1.13 (1.04-1.24)	0.0060

Supplementary Table 3 SNPs used in further analysis with information on genotype certainty.

RsID	WTCCC2			Information			TASC	MACH r^2	Call rate
	AS	1958BC	NBS	AS	1958BC	NBS			
rs11209026	Genotyped	Genotyped	Genotyped	0.997	0.999	0.998	Genotyped	-	0.994
rs2297909	Genotyped	Genotyped	Genotyped	0.998	1	1	Genotyped	-	0.991
rs10865331	Genotyped	Genotyped	Genotyped	1	1	0.999	Genotyped	-	1.00
rs30187	Genotyped	Genotyped	Genotyped	1	1	1	Genotyped	-	1.00
rs378108	Genotyped	Genotyped	Genotyped	1	1	1	Genotyped	-	1.00
rs11249215	Imputed	Genotyped	Genotyped	0.947	0.999	0.999	Imputed	0.833	-
rs6556416	Imputed	Imputed	Imputed	0.989	0.995	0.995	Imputed	0.915	-
rs11616188	Imputed	Imputed	Imputed	0.856	0.971	0.971	Imputed	0.661	-
rs10440635	Imputed	Genotyped	Genotyped	0.991	1	1	Imputed	0.993	-
rs10781500	Genotyped	Genotyped	Genotyped	1	1	1	Imputed	0.989	-
rs8070463	Imputed	Genotyped	Genotyped	0.974	1	0.999	Imputed	0.956	-

rs4389526	Imputed	Imputed	Imputed	0.993	0.996	0.996	Imputed	0.999	-
rs11209032	Genotyped	Genotyped	Genotyped	0.999	1	1	Genotyped	-	1.00
rs10050860	Genotyped	Genotyped	Genotyped	0.999	1	0.999	Genotyped	-	0.999
rs4349859 ^a	Imputed	Imputed	Imputed	0.991			Imputed	0.989	-

^aThis SNP was genotyped using MACH

Supplementary Table 4 rs4349859 genotypes in cases and controls, grouped by HLA-B27 subtype, country or region of origin, and affection status

Supplementary Table 4a Findings in British and Australian cases and controls.

		rs4349859 genotype		
HLA-B27 TYPE/SUBTYPE	AFFECTION STATUS	AA	AG	GG
B*27 NEGATIVE	CONTROL	0	4	673
B*27 NEGATIVE	CASE	0	3	47
B*27 POSITIVE	CONTROL	2	62	0
B*27 POSITIVE	CASE	20	457	11

Supplementary Table 4b Findings in AS cases and controls with B*27 subtype data available, by country or region of origin.

		rs4349859 genotype			Country or Region of origin
HLA-B27 TYPE/SUBTYPE	AFFECTION STATUS	AA	AG	GG	
B*27 NEGATIVE	CONTROL	0	1	49	Sardinia
*2702	CONTROL	0	3	0	Sardinia
*2702	CASE	0	5	0	Sardinia
*2705	CONTROL	1	57	0	Sardinia
*2705	CASE	3	89	3	Sardinia
*2707	CASE	0	0	4	Sardinia
*2707	CONTROL	0	0	4	Sardinia
*2709	CONTROL	0	30	0	Sardinia

*2713	CASE	1	1	0	Sardinia
B*27 NEGATIVE	CONTROL	0	0	23	The Azores, Portugal
*2703	CONTROL	0	1	3	African
*2707	CONTROL	0	0	2	The Azores, Portugal
*2708	CASE	0	2	0	The Azores, Portugal
*2708	CONTROL	0	2	0	The Azores, Portugal
B*27 NEGATIVE	CONTROL	0	0	50	Shanghai, China
*2704	CONTROL	0	2	28	Shanghai, China
*2704	CASE	0	0	71	Shanghai, China
*2705	CONTROL	0	15	2	Shanghai, China
*2705	CASE	0	17	2	Shanghai, China
*2710	CONTROL	0	1	1	Shanghai, China
*2706	CONTROL	0	0	7	Thai
*2707	CASE	0	0	2	Thai
*2707	CASE	0	1	2	Indian

Supplementary Table 5 Results of the interaction analyses for unlinked loci sorted according to combined P value.

Marker 1	Coded Allele ¹ Marker 1	Marker 2	Coded Allele ¹ Marker2	WTCCC2 P value	TASC P value	Replication P value	Interaction Regression Coefficient ²	SE	Combined P value
rs30187	T	rs4349859	A	0.024	0.014	0.0019	0.35	0.079	7.3x10 ⁻⁶
rs10050860	T	rs4349859	A	0.10	0.070	0.0010	-0.36	0.090	6.3x10 ⁻⁵
rs30187	T	rs10781500	T	0.038	0.0043	0.46	0.11	0.035	0.0016
rs10781500	T	rs11616188	G	0.89	0.0091	0.071	-0.093	0.036	0.011
rs10865331	G	rs4349859	A	0.19	0.21	0.20	0.16	0.073	0.027
rs11209026	G	rs8070463	T	0.30	0.27	0.095	0.19	0.085	0.029
rs10440635	G	rs8070463	T	0.056	0.33	0.37	-0.076	0.035	0.030
rs10050860	T	rs11616188	G	0.32	0.93	0.018	0.096	0.047	0.038
rs4349859	A	rs11616188	G	0.12	0.48	0.033	-0.15	0.077	0.048
rs11209026	G	rs10865331	G	0.61	0.22	0.078	-0.17	0.084	0.049
rs4389526	T	rs10781500	T	0.78	0.54	0.018	-0.069	0.036	0.056
rs2297909	G	rs10865331	G	0.71	0.18	0.14	0.067	0.038	0.075
rs10865331	G	rs4389526	T	0.14	0.78	0.43	0.055	0.036	0.13

rs10865331	G	rs8070463	T	0.58	0.24	0.34	-0.053	0.035	0.13
rs11209026	G	rs10781500	T	0.027	0.90	0.79	-0.13	0.083	0.13
rs11249215	G	rs10865331	G	0.44	0.76	0.18	-0.050	0.034	0.15
rs10050860	T	rs378108	G	0.72	0.057	0.66	-0.062	0.043	0.15
rs2297909	G	rs8070463	T	0.25	0.80	0.41	0.051	0.038	0.18
rs11209032	G	rs6556416	C	0.14	0.51	0.90	-0.051	0.038	0.19
rs11209026	G	rs378108	G	0.94	0.014	0.71	-0.10	0.082	0.20
rs10440635	G	rs10781500	T	0.75	0.89	0.033	-0.042	0.035	0.23
rs10050860	T	rs10781500	T	0.80	0.52	0.26	-0.051	0.044	0.24
rs2297909	G	rs10781500	T	0.90	0.19	0.33	-0.044	0.038	0.25
rs2297909	G	rs378108	G	0.065	0.19	0.30	0.043	0.038	0.25
rs11209032	G	rs30187	T	0.90	0.51	0.22	-0.042	0.037	0.25
rs30187	T	rs11616188	G	0.61	0.61	0.36	-0.043	0.038	0.26
rs11209026	G	rs10050860	T	0.45	0.83	0.20	0.12	0.11	0.26
rs11209026	G	rs4349859	A	0.75	0.90	0.15	0.19	0.17	0.26
rs11249215	G	rs11209026	G	0.44	0.072	0.76	0.092	0.083	0.27
rs10440635	G	rs11616188	G	0.45	0.66	0.51	0.040	0.037	0.28

rs6556416	C	rs8070463	T	0.98	0.13	0.59	0.039	0.037	0.29
rs4389526	T	rs8070463	T	0.65	0.28	0.23	-0.036	0.036	0.31
rs11249215	G	rs11616188	G	0.23	0.83	0.49	0.037	0.037	0.32
rs11249215	G	rs10440635	G	0.37	0.35	0.093	-0.035	0.035	0.32
rs10781500	T	rs8070463	T	0.40	0.19	0.78	0.034	0.035	0.32
rs4349859	A	rs378108	G	0.49	0.75	0.057	0.070	0.073	0.34
rs11209026	G	rs6556416	C	0.65	0.76	0.42	0.082	0.089	0.36
rs10050860	T	rs8070463	T	0.22	0.49	0.77	-0.040	0.044	0.36
rs11249215	G	rs4349859	A	0.46	0.36	1.00	-0.064	0.074	0.39
rs11209026	G	rs2297909	G	0.95	0.42	0.40	-0.076	0.091	0.40
rs30187	T	rs378108	G	0.80	0.14	0.69	0.029	0.035	0.41
rs2297909	G	rs10440635	G	0.053	0.28	0.15	0.032	0.038	0.41
rs4349859	A	rs10781500	T	0.36	0.34	0.27	0.059	0.073	0.42
rs30187	T	rs6556416	C	0.16	1.00	0.93	0.031	0.039	0.42
rs11209032	G	rs8070463	T	0.99	1.00	0.21	-0.028	0.036	0.44
rs10050860	T	rs6556416	C	0.29	0.46	0.67	-0.036	0.047	0.45
rs11209032	G	rs378108	G	0.086	0.67	0.90	-0.026	0.035	0.46

rs11209032	G	rs2297909	G	0.58	0.16	0.61	0.028	0.039	0.47
rs6556416	C	rs11616188	G	0.15	0.88	0.98	-0.028	0.039	0.47
rs10865331	G	rs10050860	T	0.16	0.68	0.51	0.029	0.044	0.50
rs10440635	G	rs6556416	C	0.99	0.67	0.16	0.025	0.038	0.51
rs4349859	A	rs8070463	T	0.26	0.18	0.32	-0.047	0.072	0.51
rs11249215	G	rs4389526	T	0.61	0.80	0.45	-0.024	0.037	0.52
rs4389526	T	rs30187	T	0.71	0.95	0.46	-0.024	0.038	0.52
rs10865331	G	rs30187	T	0.99	0.22	0.97	-0.023	0.036	0.52
rs4389526	T	rs378108	G	0.11	0.51	0.93	-0.022	0.036	0.54
rs6556416	C	rs378108	G	0.76	0.87	0.59	-0.022	0.037	0.55
rs11209032	G	rs10440635	G	0.65	0.44	0.89	-0.021	0.036	0.56
rs10865331	G	rs11616188	G	0.60	0.35	0.25	-0.021	0.037	0.57
rs4389526	T	rs4349859	A	0.44	0.56	0.61	-0.041	0.076	0.59
rs11249215	G	rs378108	G	0.33	0.95	0.074	-0.017	0.035	0.62
rs2297909	G	rs4389526	T	0.94	0.62	0.73	-0.020	0.040	0.62
rs6556416	C	rs10781500	T	0.54	0.048	0.16	0.018	0.037	0.64
rs11249215	G	rs2297909	G	0.93	0.67	0.62	0.018	0.038	0.64

rs11209032	G	rs10050860	T	0.20	0.47	0.25	-0.020	0.045	0.65
rs11616188	G	rs8070463	T	0.61	0.99	0.88	0.014	0.036	0.70
rs11209032	G	rs4349859	A	0.38	0.48	0.37	-0.028	0.076	0.72
rs10865331	G	rs6556416	C	0.57	0.95	0.95	-0.013	0.037	0.73
rs10865331	G	rs10781500	T	0.71	0.074	0.11	0.011	0.034	0.74
rs11209026	G	rs4389526	T	0.064	0.65	0.23	-0.028	0.087	0.74
rs2297909	G	rs10050860	T	0.44	0.22	0.72	-0.016	0.048	0.75
rs2297909	G	rs4349859	A	0.61	0.99	0.33	0.025	0.080	0.75
rs11209032	G	rs4389526	T	0.17	0.74	0.55	-0.012	0.037	0.76
rs10781500	T	rs378108	G	0.92	0.63	0.85	0.010	0.034	0.77
rs4389526	T	rs10050860	T	0.85	0.29	0.14	0.013	0.046	0.77
rs11209026	G	rs10440635	G	0.83	0.53	0.81	0.024	0.084	0.78
rs4389526	T	rs6556416	C	0.82	0.059	0.41	-0.011	0.039	0.79
rs10865331	G	rs378108	G	0.37	0.59	0.39	-0.009	0.034	0.79
rs2297909	G	rs30187	T	1.00	0.42	0.83	0.010	0.039	0.79
rs10865331	G	rs10440635	G	0.012	0.88	0.048	0.009	0.035	0.80
rs11249215	G	rs10781500	T	0.87	0.95	0.62	-0.009	0.035	0.81

rs4389526	T	rs10440635	G	0.014	0.22	0.31	0.009	0.036	0.81
rs30187	T	rs8070463	T	0.31	0.34	0.55	0.008	0.036	0.81
rs2297909	G	rs6556416	C	0.48	0.75	0.92	-0.009	0.041	0.82
rs11249215	G	rs6556416	C	0.30	0.66	0.33	0.008	0.038	0.82
rs11209032	G	rs11616188	G	0.59	0.73	0.62	0.007	0.038	0.85
rs6556416	C	rs4349859	A	0.85	0.23	0.19	-0.014	0.079	0.86
rs10440635	G	rs30187	T	0.43	0.34	0.80	-0.006	0.036	0.86
rs11209026	G	rs30187	T	0.46	0.30	0.79	0.014	0.082	0.86
rs11249215	G	rs8070463	T	0.70	0.52	0.26	0.006	0.034	0.87
rs2297909	G	rs11616188	G	0.47	0.35	0.75	-0.007	0.041	0.87
rs11209026	G	rs11616188	G	0.098	0.390	0.52	-0.014	0.088	0.87
rs11249215	G	rs10050860	T	0.26	0.62	0.65	-0.007	0.045	0.87
rs11616188	G	rs378108	G	0.90	0.32	0.27	0.005	0.036	0.88
rs11249215	G	rs30187	T	0.90	0.75	0.55	0.005	0.036	0.90
rs8070463	T	rs378108	G	0.90	0.50	0.39	-0.004	0.034	0.91
rs4389526	T	rs11616188	G	0.64	0.86	0.53	0.003	0.038	0.94
rs11249215	G	rs11209032	G	0.80	0.83	0.86	-0.002	0.036	0.95

rs10440635	G	rs10050860	T	0.72	0.72	0.86	0.003	0.044	0.95
rs11209032	G	rs10781500	T	0.49	0.41	0.93	-0.002	0.035	0.95
rs10440635	G	rs378108	G	0.47	0.94	0.39	0.002	0.035	0.96
rs11209032	G	rs10865331	G	0.56	0.72	0.36	-0.001	0.036	0.98

1 Coded allele refers to the allele that was coded as 2 in the logistic regression

2 The regression coefficient is for the additive x additive interaction term in the logistic regression model

A dominant model was used for rs4349859 (see main text).

Supplementary Table 6 Association findings in cases and controls stratified by HLA-B27 status, inferred from rs4349859 genotype. Given the association of these SNPs with overall disease, genome-wide levels of significance are not appropriate for tests in disease subtypes.

rsID	Candidate gene	Effect Allele	Inferred B27 status	WTCCC2		TASC		Replication		Combined	
				OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
rs11249215	<i>RUNX3</i>	A	+ve	1.16 (0.99-1.36)	0.070	1.27 (1.03-1.56)	0.023	1.16 (0.98-1.36)	0.079	1.18 (1.07-1.31)	0.00094
rs11249215	<i>RUNX3</i>	A	-ve	1.06 (0.88-1.27)	0.55	1.05 (0.81-1.35)	0.71	1.16 (1-1.34)	0.046	1.11 (1-1.23)	0.055
rs4389526	<i>ANTXR2</i>	A	+ve	1.13 (0.96-1.33)	0.15	1.11 (0.91-1.36)	0.29	1.09 (0.92-1.29)	0.31	1.11 (1-1.23)	0.041
rs4389526	<i>ANTXR2</i>	A	-ve	1.02 (0.85-1.23)	0.81	1.25 (0.97-1.61)	0.081	1.01 (0.87-1.18)	0.89	1.05 (0.95-1.17)	0.33
rs10440635	<i>PTGER4</i>	A	+ve	1.13 (0.97-1.32)	0.13	1.49 (1.24-1.8)	2.6x10 ⁻⁵	1.07 (0.91-1.26)	0.41	1.19 (1.08-1.31)	0.00035
rs10440635	<i>PTGER4</i>	A	-ve	1.01 (0.84-1.21)	0.93	0.96 (0.76-1.22)	0.74	0.93 (0.8-1.08)	0.34	0.96 (0.87-1.06)	0.45
rs6556416	<i>IL12B</i>	A	+ve	0.84 (0.71-0.99)	0.044	0.85 (0.68-1.05)	0.13	0.87 (0.73-1.04)	0.13	0.86 (0.77-0.95)	0.0034
rs6556416	<i>IL12B</i>	A	-ve	0.86 (0.71-1.05)	0.14	1.02 (0.78-1.33)	0.92	0.75 (0.64-0.89)	0.00049	0.83 (0.74-0.93)	0.0014
rs10781500	<i>CARD9</i>	C	+ve	0.75 (0.64-0.88)	0.00030	1.01 (0.84-1.22)	0.89	0.98 (0.83-1.16)	0.83	0.89 (0.81-0.98)	0.023
rs10781500	<i>CARD9</i>	C	-ve	0.84 (0.7-1)	0.051	1.13 (0.01-131.82)	0.12	1.1 (0.95-1.28)	0.20	0.98 (0.88-1.1)	0.77
rs11616188	<i>LTBR-TNFRSF1A</i>	A	+ve	1.56 (1.31-1.86)	3.6x10 ⁻⁷	1.23 (0.97-1.55)	0.084	1.24 (1.05-1.46)	0.0093	1.35 (1.21-1.5)	3.3x10 ⁻⁸

rs11616188	<i>LTBR-TNFRSF1A</i>	A	-ve	1.26 (1.02-1.55)	0.035	1.16 (1.05-1.28)	0.0023	0.99 (0.85-1.15)	0.90	1.07 (0.95-1.21)	0.27
rs8070463	<i>TBKBP1</i>	C	+ve	1.23 (1.05-1.43)	0.0097	1.21 (1-1.47)	0.052	1 (0.85-1.17)	0.98	1.13 (1.03-1.25)	0.011
rs8070463	<i>TBKBP1</i>	C	-ve	1.07 (0.89-1.28)	0.49	1.02 (0.8-1.29)	0.88	1.12 (0.97-1.29)	0.13	1.08 (0.98-1.2)	0.13
rs11209026	<i>IL23R</i>	A	+ve	0.57 (0.42-0.78)	0.00078	0.6 (0.38-0.95)	0.029	0.52 (0.37-0.74)	0.00044	0.56 (0.45-0.69)	4.5x10 ⁻⁸
rs11209026	<i>IL23R</i>	A	-ve	0.63 (0.4-0.97)	0.024	0.56 (0.31-1.04)	0.065	0.77 (0.54-1.08)	0.12	0.68 (0.53-0.87)	0.0024
rs11209032	<i>IL23R</i>	A	+ve	1.23 (1.05-1.45)	0.012	1.28 (1.05-1.58)	0.017	1.39 (1.16-1.67)	0.00030	1.3 (1.17-1.44)	1.2x10 ⁻⁶
rs11209032	<i>IL23R</i>	A	-ve	1.38 (1.15-1.65)	0.00057	1.13 (0.88-1.44)	0.34	1.25 (1.07-1.45)	0.0042	1.27 (1.14-1.4)	9.6x10 ⁻⁶
rs2297909	<i>KIF21B</i>	A	+ve	0.94 (0.79-1.11)	0.45	0.8 (0.65-0.99)	0.039	0.75 (0.62-0.9)	0.0019	0.83 (0.75-0.93)	0.00075
rs2297909	<i>KIF21B</i>	A	-ve	0.88 (0.72-1.06)	0.17	0.81 (0.61-1.06)	0.12	0.85 (0.72-1)	0.050	0.85 (0.76-0.95)	0.0055
rs10865331	2p15 intergenic	A	+ve	1.17 (1-1.37)	0.043	1.23 (1.01-1.49)	0.042	1.29 (1.09-1.53)	0.0034	1.23 (1.11-1.35)	6.3x10 ⁻⁵
rs10865331	2p15 intergenic	A	-ve	1.38 (1.15-1.64)	0.00042	1.46 (1.16-1.85)	0.0013	1.49 (1.29-1.73)	1.3x10 ⁻⁷	1.45 (1.31-1.6)	1.3x10 ⁻¹²
rs10050860	<i>ERAP1</i>	A	+ve	0.71 (0.59-0.86)	0.00039	0.66 (0.51-0.84)	0.0010	0.64 (0.52-0.78)	3.1x10 ⁻⁵	0.67 (0.59-0.76)	1.5x10 ⁻¹⁰
rs10050860	<i>ERAP1</i>	A	-ve	0.9 (0.73-1.12)	0.35	0.97 (0.72-1.3)	0.82	1.02 (0.86-1.22)	0.81	0.97 (0.86-1.1)	0.65
rs30187	<i>ERAP1</i>	A	+ve	1.36 (1.15-1.61)	0.00032	1.51 (1.22-1.87)	0.0001	1.48 (1.22-1.78)	4.7x10 ⁻⁵	1.44 (1.29-1.6)	6.2x10 ⁻¹¹
rs30187	<i>ERAP1</i>	A	-ve	1.02 (0.85-1.23)	0.84	0.98 (0.76-1.25)	0.84	1.01 (0.86-1.18)	0.92	1.01 (0.9-1.12)	0.92
rs378108	21q22 intergenic	A	+ve	0.81 (0.69-0.94)	0.0066	0.76 (0.63-0.92)	0.0051	0.82 (0.69-0.96)	0.016	0.8 (0.72-0.88)	5.8x10 ⁻⁶
rs378108	21q22 intergenic	A	-ve	0.74 (0.62-0.89)	0.00092	0.78 (0.62-0.99)	0.039	1 (0.86-1.16)	0.079	0.86 (0.78-0.96)	0.0051

Supplementary Table 7a Odds ratios for the nine genotype combinations at rs4349859 and rs30187 in the TASC Discovery Cohort. 95%

Confidence Intervals are presented in parentheses.

		rs4349859		
		GG	AG	AA
rs30187	CC	1	70.85 (51 - 100)	93.37 (33 - 265)
	CT	1.03 (0.72 – 1.47)	108.60 (78 - 151)	266.17 (60 - 1173)
	TT	0.99 (0.58 – 1.67)	157.27 (96 - 258)	98.03 (7.62 - 1262)

Supplementary Table 7b Odds ratios for the nine genotype combinations at rs4349859 and rs30187 in the WTCCC2 Discovery Cohort. 95%

Confidence Intervals are presented in parentheses.

		rs4349859		
		GG	AG	AA
rs30187	CC	1	47 (37 - 61)	45 (17 - 117)
	CT	0.96 (0.73 – 1.25)	73 (57 - 93)	203 (62 - 669)
	TT	1.10 (0.73 – 1.64)	75 (52 - 109)	118 (14 - 970)

Supplementary Table 7c Odds ratios for the nine genotype combinations at rs4349859 and rs30187 in the Replication Cohort. 95% Confidence

Intervals are presented in parentheses.

		rs4349859		
		GG	AG	AA
rs30187	CC	1	33 (25 - 42)	75 (22 - 254)
	CT	1.12 (0.90 – 1.40)	54 (42 - 68)	105 (32 - 349)
	TT	0.92 (0.65 – 1.32)	63 (42 - 95)	NA*

*Number of control individuals with this genotype are too small to obtain accurate odds ratio estimates

Supplementary Table 7d Odds ratios for the nine genotype combinations at rs4349859 and rs30187 in the Combined Cohort. 95% Confidence Intervals are presented in parentheses.

		rs4349859		
		GG	AG	AA
rs30187	CC	1	45 (39 - 53)	63 (34 - 115)
	CT	1.05 (0.90 – 1.22)	71 (61 - 83)	171 (82 - 356)
	TT	0.98 (0.78 – 1.25)	85 (67 - 107)	129 (28 - 592)

Supplementary Table 7e Odds ratios for genotype combinations at rs4349859 and rs30187 in the TASC Discovery Cohort. Rs4349859 has been coded according to a dominant mode of inheritance. 95% Confidence Intervals are presented in parentheses.

		rs4349859	
		GG	AG/AA
rs30187	CC	1	72 (51 - 101)
	CT	1.03 (0.72 – 1.47)	111 (80 - 155)
	TT	0.99 (0.58 – 1.68)	156 (96 - 254)

Supplementary Table 7f Odds ratios for genotype combinations at rs4349859 and rs30187 in the WTCCC2 Discovery Cohort. Rs4349859 has been coded according to a dominant mode of inheritance. 95% Confidence Intervals are presented in parentheses.

		rs4349859	
		GG	AG/AA
rs30187	CC	1	47 (37 - 61)
	CT	0.96 (0.73 – 1.25)	75 (58 - 96)
	TT	1.10 (0.73 – 1.64)	76 (53 - 110)

Supplementary Table 7g Odds ratios for genotype combinations at rs4349859 and rs30187 in the Replication Cohort. Rs4349859 has been coded according to a dominant mode of inheritance. 95% Confidence Intervals are presented in parentheses.

		rs4349859	
		GG	AG/AA
rs30187	CC	1	33 (26 - 43)
	CT	1.12 (0.90 – 1.40)	55 (43 - 69)
	TT	0.92 (0.65 – 1.31)	65 (43 - 97)

Supplementary Table 7h Combined Dominant Odds ratios for genotype combinations at rs4349859 and rs30187 in the Combined Cohort. Rs4349859 has been coded according to a dominant mode of inheritance. 95% Confidence Intervals are presented in parentheses.

		rs4349859	
		GG	AG/AA
rs30187	CC	1	46 (39 - 53)
	CT	1.05 (0.90 – 1.22)	73 (63 - 85)
	TT	0.98 (0.78 – 1.25)	85 (67 - 108)

Supplementary Table 8 Breakdown of individual sample quality control exclusions pre-imputation.

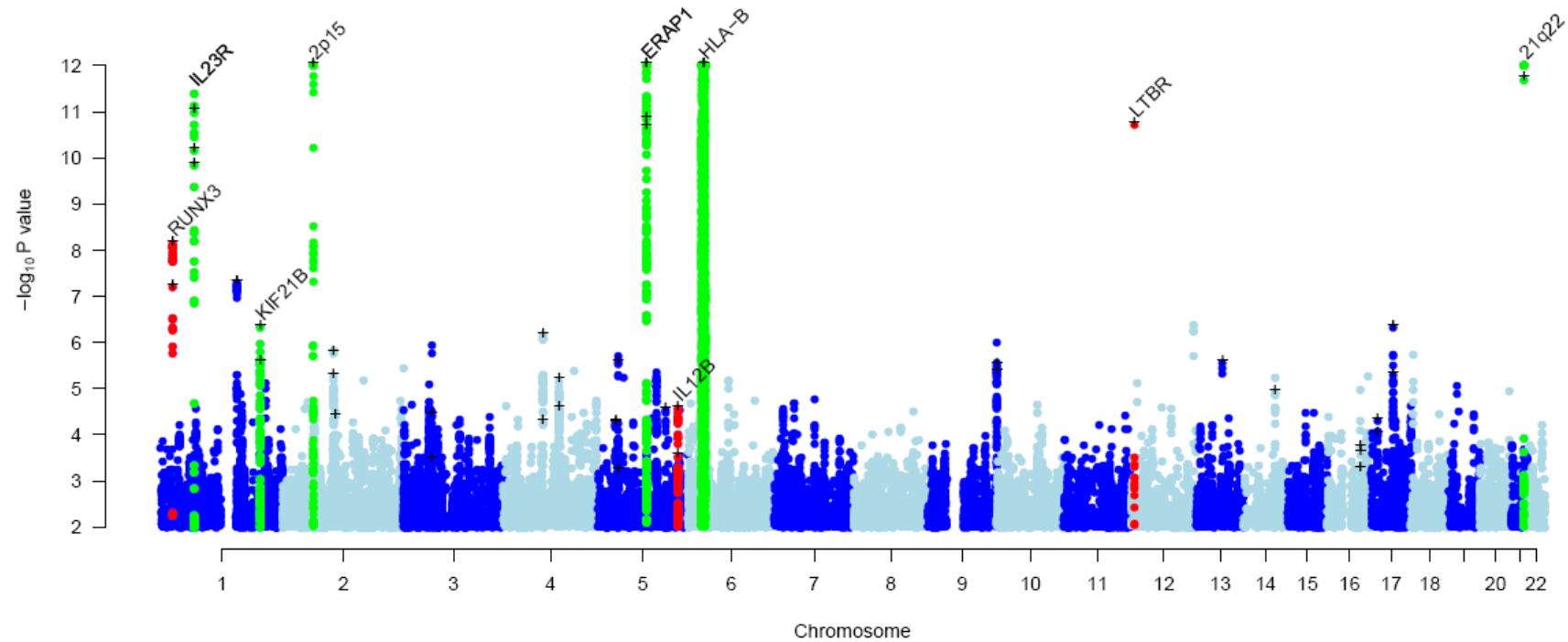
	QC	Ancestry	Relatedness	Gender	Intensity	Identity	Total	Remaining
AS	94	41	86	4	3	3	218	1787
1958BC	137	57	24	11	32	1	261	2492
UKBS	111	51	60	14	23	8	244	2324

Numbers of individuals excluded, where column headings are, QC: call rate and heterozygosity, Ancestry: HapMap PCA population exclusions, Relatedness: >5%IBD, Gender: gender modeled from X chromosome intensity discordant with supplier gender, Intensity: outlying channel intensity, Identity: <90% concordant with initial genotypes, Total: the number of unique samples excluded, Remaining: the number of samples carried through to the analysis stage.

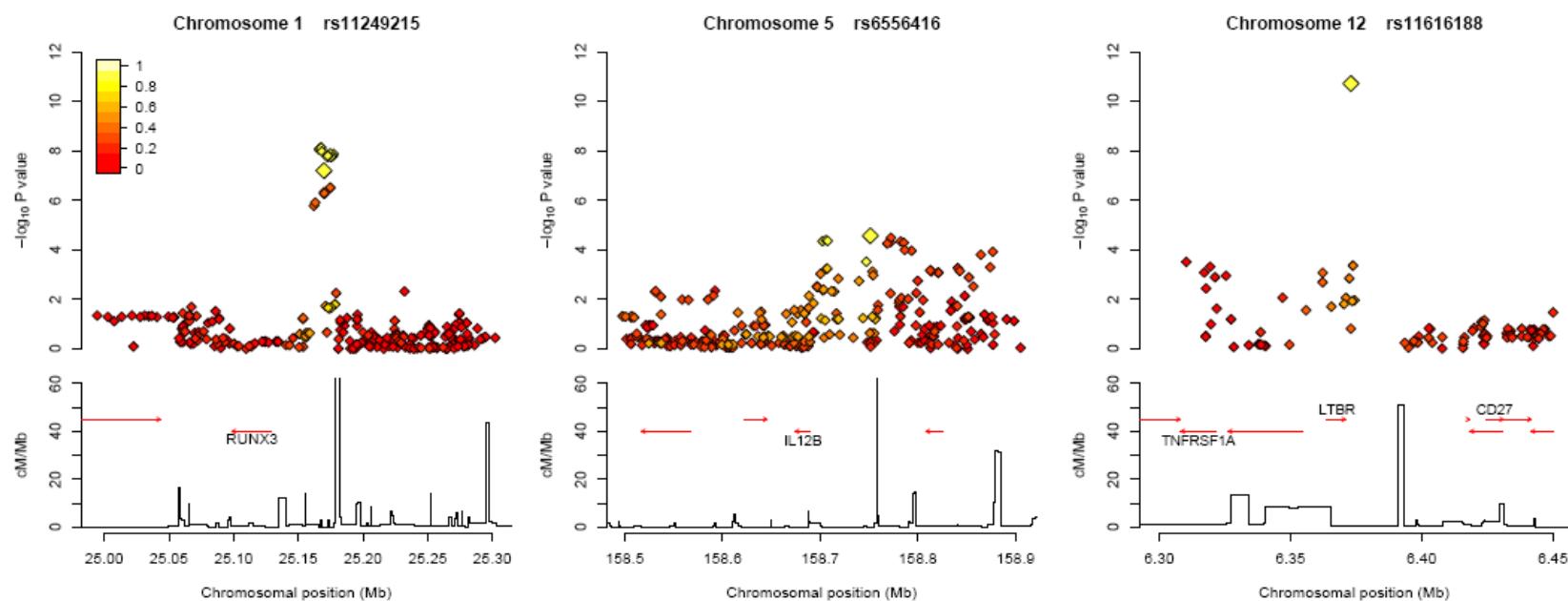
Supplementary Table 9 Genome-wide inflation factor

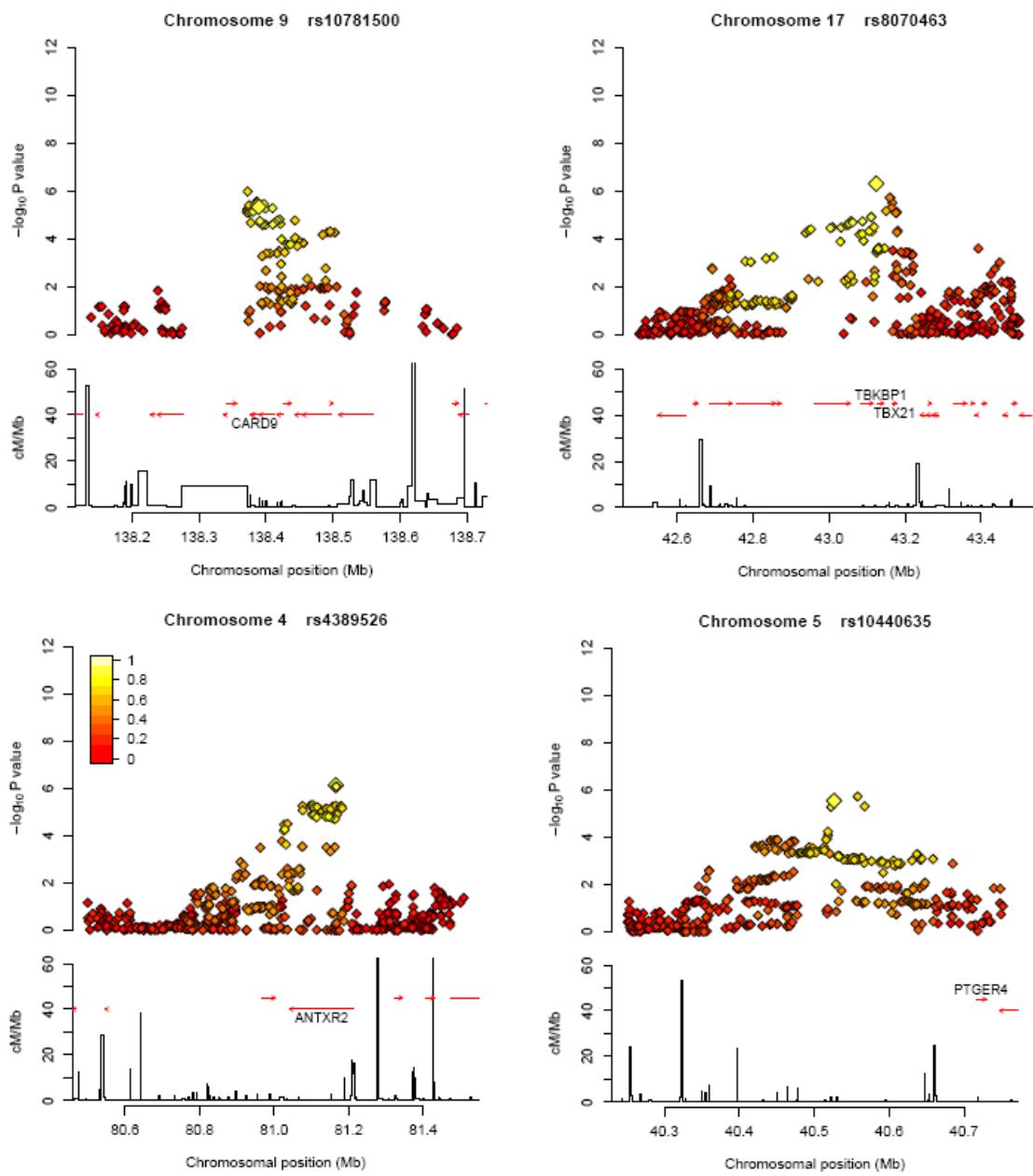
	Genome	No MHC	No MHC or Regions in Table 1
TASC	1.025	1.0178	1.0160
WTCCC2	1.056	1.0478	1.0444
Combined	1.084	1.0755	1.0713

Supplementary Figure 1 Manhattan plot of WTCCC2-TASC discovery set association study findings.



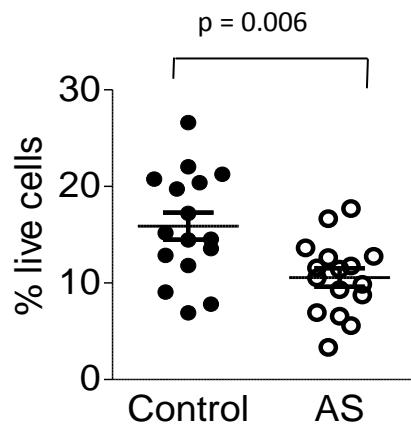
Supplementary Figure 2 Regional association plots. The $-\log_{10} P$ values for the SNPs at the 7 new loci are shown in the upper part of each plot. SNPs are colored based on their linkage disequilibrium (r^2 , calculated from the 58C control data) with the labeled hit SNP which has the smallest P value in the region. The bottom section of each plot shows the fine scale recombination rates estimated from individuals in the HapMap population, and genes are marked by horizontal red lines.





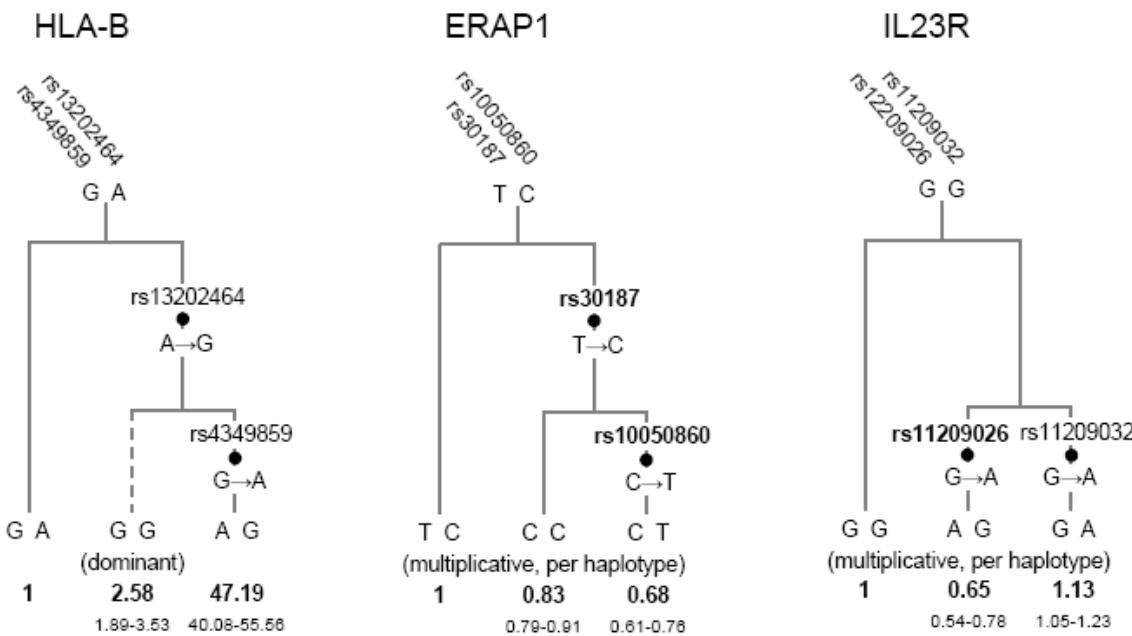
Supplementary Figure 3 CD8⁺ T cells are reduced in the peripheral blood of AS patients.

PBMC from patients with active AS and age-matched healthy controls (n = 16 for both groups) were stained for cell surface T cell markers and analysed by flow cytometry. Circulating CD8⁺ T cells (CD3⁺CD8⁺) were significantly reduced in AS patients (mean = 10.57% ± 0.96) compared with controls (mean = 15.89% ± 1.4) (p = 0.006, Mann Whitney U two-tailed test).

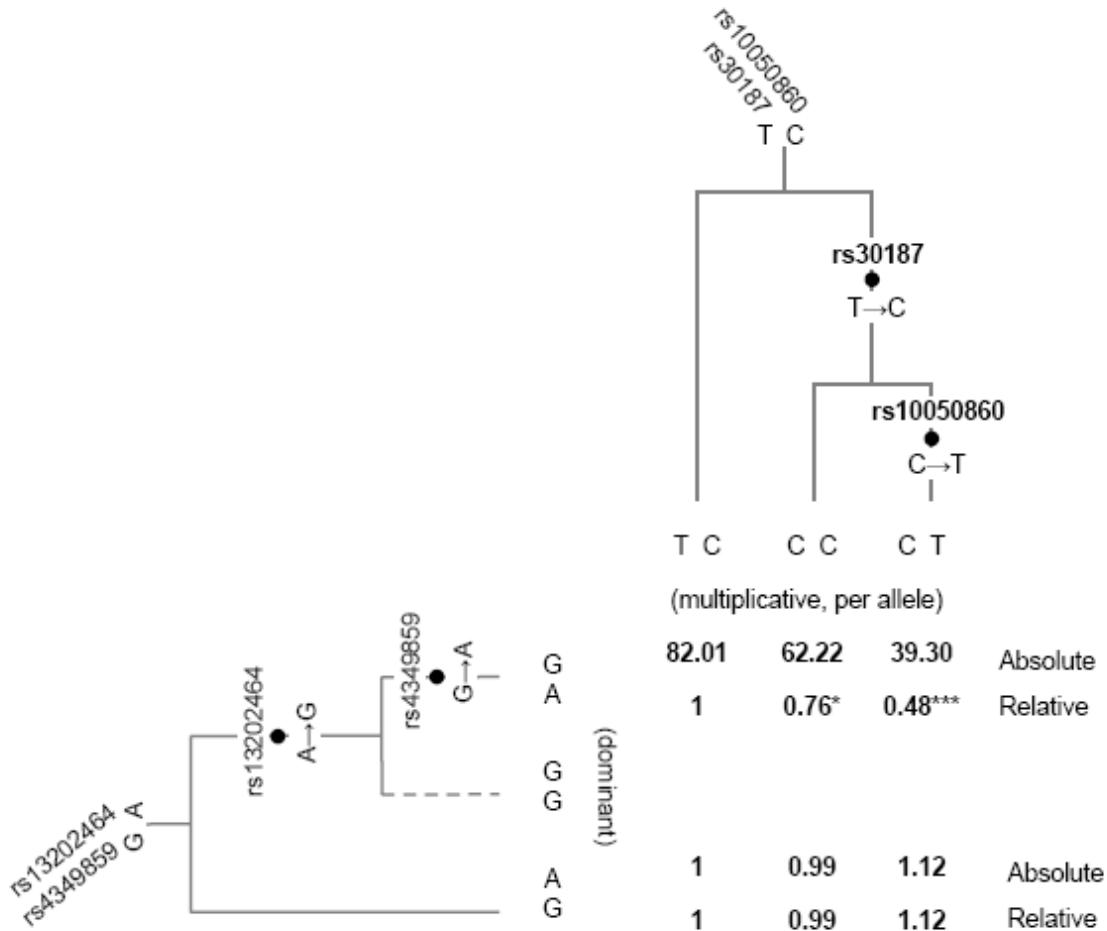


Supplementary Figure 4 Ancestral trees describing the haplotype risks at loci exhibiting secondary signals of association.

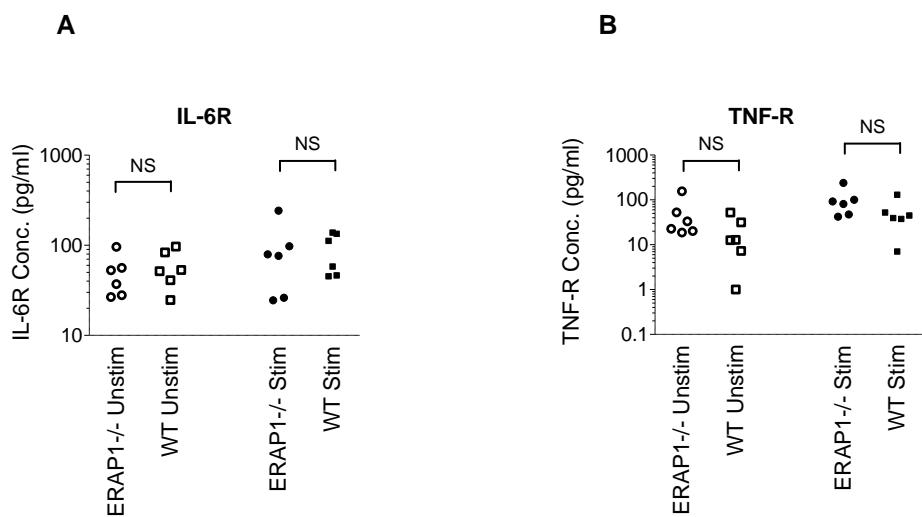
A. For each pair of SNPs in the HLA-B, *IL23R* and *ERAP1* regions, the genotypes were consistent with only 3 haplotypes, suggesting little or no recombination events (<10 potential recombinants were removed from the data in each case). Using primate sequences the ancestral alleles were identified (<http://www.ncbi.nlm.nih.gov/projects/SNP/>) at both SNPs, allowing the construction of the ancestral tree on which the mutation which generated the haplotypes is indicated. At the bottom of the trees are the estimated odds ratio (and 95%CI) for each of the haplotypes (either assuming an additive or dominant model). Non-synonymous mutation events are indicated in bold. Risks were estimated from the replication sample (see text).



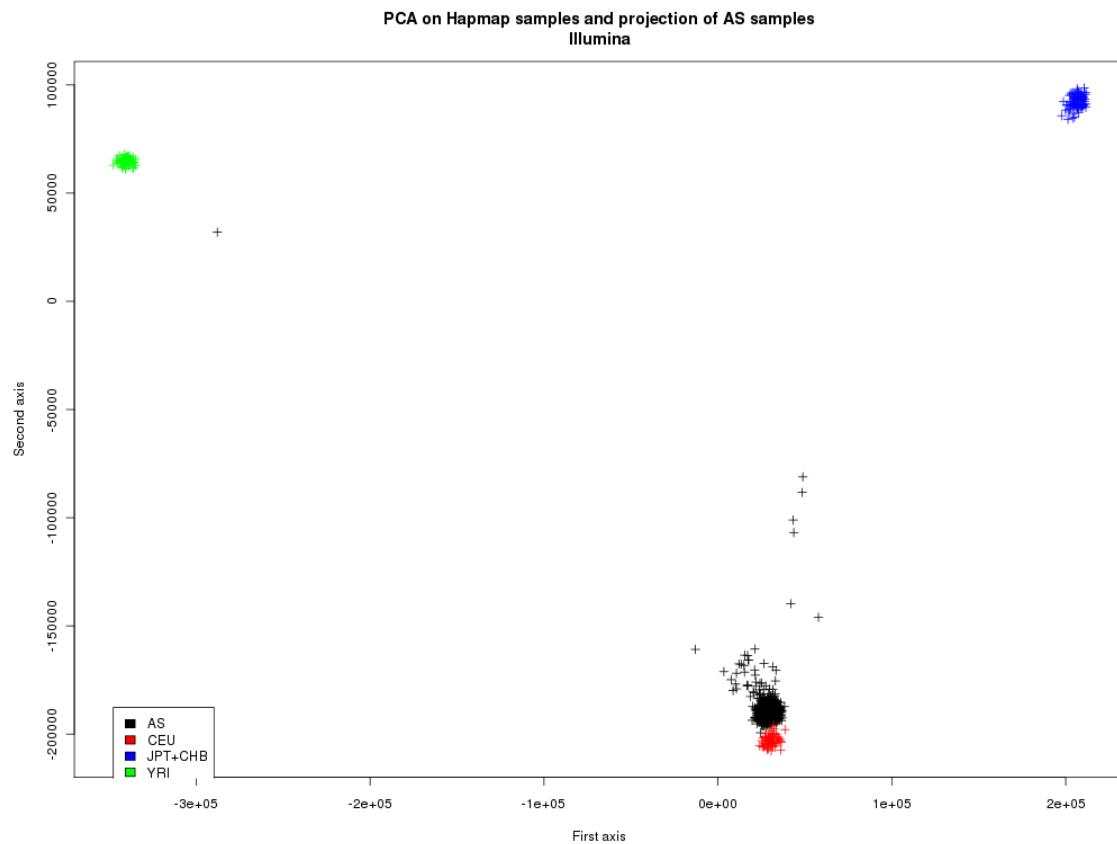
B. Haplotype interaction model at HLA-B and *ERAP1*. The table and accompanying ancestral trees show the absolute and relative risk of the three haplotypes at *ERAP1* in individuals carrying at least one copy of the risk haplotype at HLA-B (HLA-B27-positive), and in individuals who are homozygote for the protective allele (HLA-B27-negative). Note that there is no evidence the *ERAP1* haplotypes influence risk in HLA-B27-negative individuals, whereas in HLA-B27-positive individuals, the most protective *ERAP1* haplotype reduces risk by over 50% per copy. Non-synonymous mutation events are indicated in bold. Risks were estimated from the replication sample.



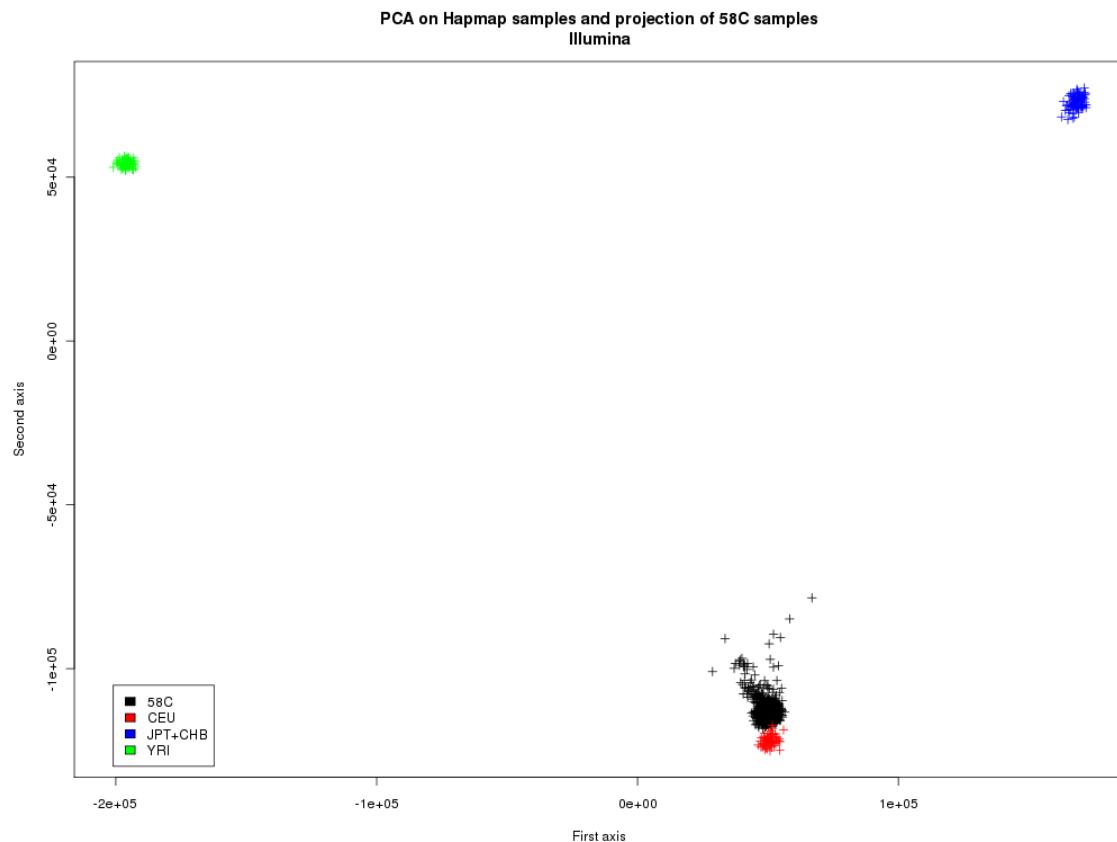
Supplementary Figure 5 Cytokine receptor cleavage is not altered in ERAP^{-/-} mice. Single cell suspensions prepared from ERAP^{-/-} (ERAP) and C57BL/6 control (WT) spleens were stimulated with or without 10 μ g/ml plate-bound anti-CD3 and 10ng/ml PMA for 24 hours. Levels of soluble IL-6R (A) and TNF-R (B) in the supernatants were determined by ELISA. Data are pooled from 2 independent experiments. Statistical significance was determined using Mann Whitney U two-tailed test. p<0.05 was considered significant.



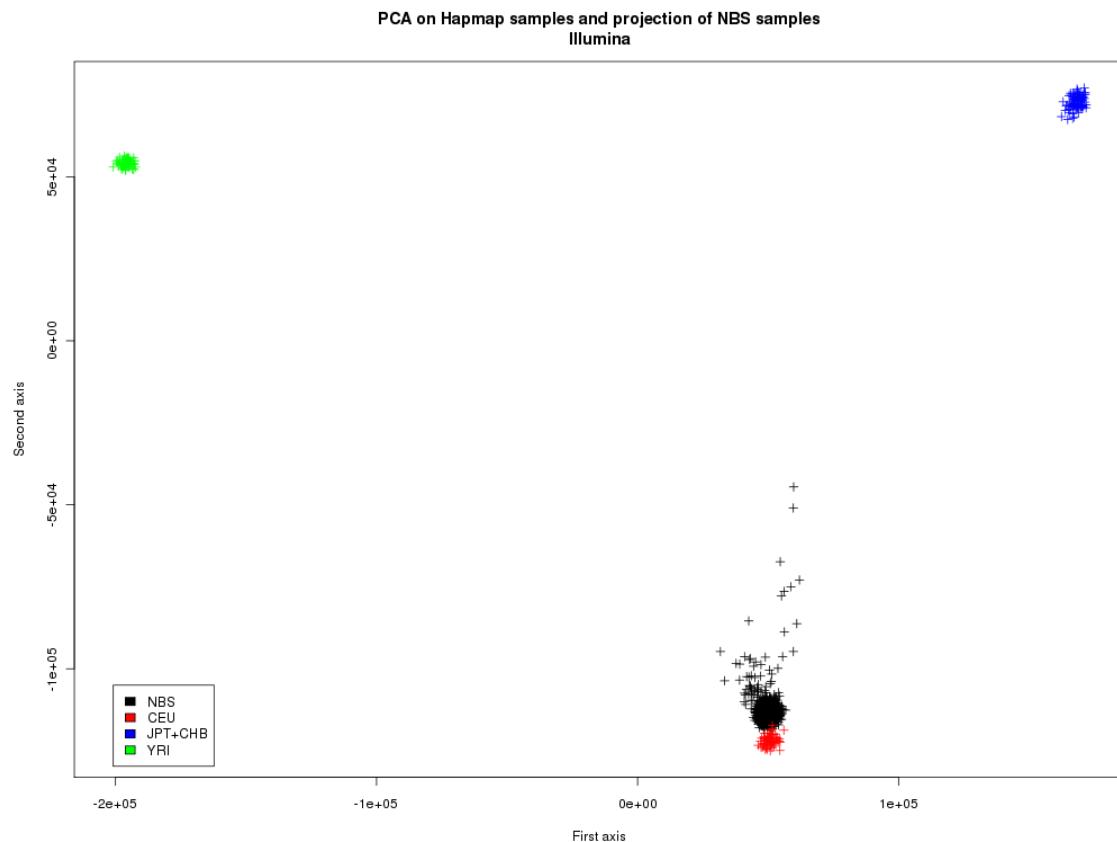
Supplementary Figure 6a Principal components analysis of WTCCC2 AS samples seeded with individuals from HapMap 2.



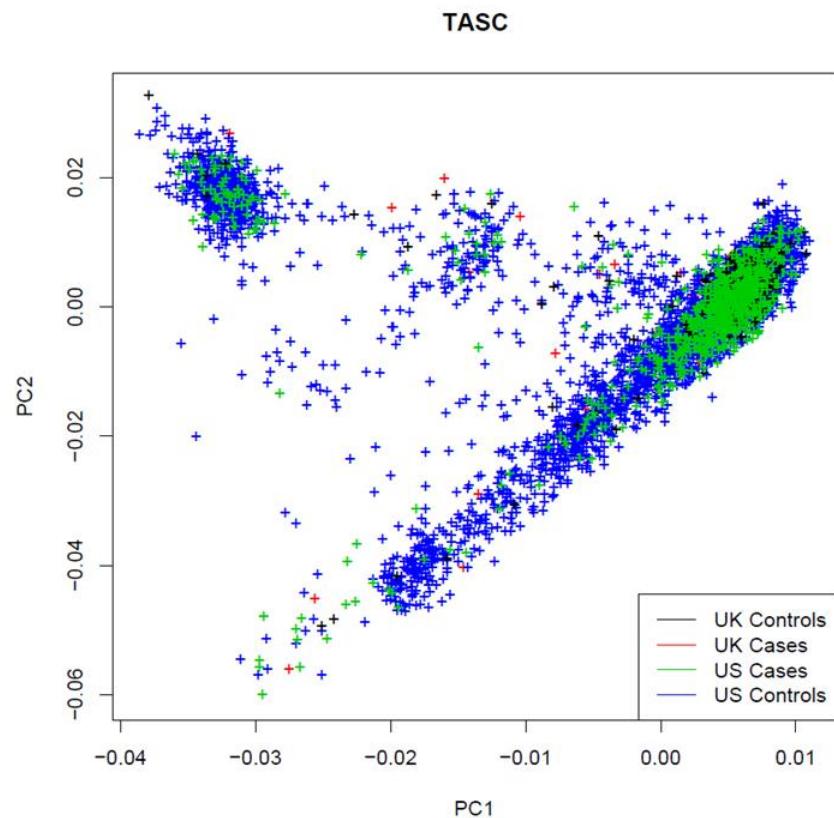
Supplementary Figure 6b Principal components analysis of WTCCC2 58BC samples seeded with individuals from HapMap 2.



Supplementary Figure 6c Principal components analysis of WTCCC2 UKBS samples seeded with individuals from HapMap 2.



Supplementary Figure 6d Principal components analysis of TASC samples. Individuals are plotted for the first two principal components.



Supplementary Figure 6e Principal components analysis of TASC samples. Individuals are plotted for principal components three and four.

